REMARKS

Status of the Application

Claims 29-49 were pending in the application at the time the Office Action was mailed. Claims 32 and 33 were withdrawn as being directed to non-elected subject matter. Claims 29-31 and 34-49 are currently under examination on the merits. Claims 29-31 and 34-49 were rejected in the Office Action. No claims were allowed.

A Request for Continued Examination (RCE) is filed herewith. By this paper, claims 29, 42, 48 and 49 are amended. New claim 50 has been added, and claims 30, 31, and 34-41 have been canceled. Support for the amendments to claim 29 and for new claim 50 can be found throughout the application as filed, e.g., previously presented claims 29 and 36 (for composition option a)), and in the Table of Example 1 of the application (for limitations b) and c)). In particular, limitations b) and c) of claim 29 as amended herein correspond to compositions B and C, respectively, of the Table in Example 1.

The amendments presented herein have been made solely to expedite prosecution of the instant application to allowance and should not be construed as an indication of Applicant's agreement with or acquiescence to the Examiner's position or as surrender of any subject matter in the instant application. Accordingly, Applicant expressly maintains the right to pursue broader subject matter through subsequent amendments, continuation or divisional applications, reexamination or reissue proceedings, and all other available means. The amendments and rejections are addressed below in more detail.

Claim Rejections - 35 U.S.C. §112

Claims 48 and 49 were rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for "a method of using a composition for the preparation of a drug for…**treatment** of psychiatric disturbances", allegedly does not reasonably provide enablement for "administration of at least another drug effective for preventing…the disturbances of CNS". According to the Office Action, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicant disagrees with this rejection, but solely in order to expedite prosecution, claims 48 and 49 have been amended herein to omit recitation of "prevention and/or" and to recite "effective for the treatment of schizophrenia" rather than "effective for the prevention and/or treatment of the disturbances of CNS."

Accordingly, withdrawal of this rejection is respectfully requested.

Claim Rejections - 35 U.S.C. §103

Claims 29-31 and 34-49 were rejected under 35 U.S.C. §103(a) as being unpatentable over Nishikawa *et al.* (U.S. Patent No. 6,306,907) and Horrobin (U.S. Patent No. 4,977,187), and further in view of Chen (U.S. Patent No. 6,759,435). The Examiner states:

> The claims differ from the cited references in claiming combination of DHA and EPA and GLA composition of Horrobin to treat schizophrenia. To employ combinations of DHA and EPA & GLA (gamma-linolenic acid: n-6 essential fatty acid) composition to treat schizophrenia would have been obvious because all the components are well known individually for treating schizophrenia. It would be expected that the combination of components would schizophrenic conditions as well. One of ordinary skill in the art would have combined the antischizophrenic agents by known methods and that in combination, each element merely would have performed the same antischizophrenic activity as it did separately.

Applicants respectfully disagree with this rejection. Solely to expedite prosecution, claims 30, 31, and 34-41 have been canceled, and claim 29 (from which claims 42-48 depend) has been amended herein to recite: a "method of using a composition, for the preparation of a drug for the treatment of schizophrenia, **consisting essentially of**, in a concentration expressed as % by weight of the total fatty acid weight in the composition, one selected from the group consisting of: a) ALA ethyl ester, wherein ALA ethyl ester is present in a concentration not lower than 70%; b) DHA ethyl ester >30 and EPA ethyl ester >44, wherein EPA+DHA ethyl esters >80, the ethyl esters of other (C20, C21, C22) n-3 acids being >3; and c) DHA ethyl ester >34 and EPA ethyl ester >40, wherein EPA+DHA ethyl esters >80, the total ethyl esters of n-3 acids being >90." Claim 49 has been amended to be an independent claim, and as amended herein, recites a "method of using a composition, for the preparation of a drug for the treatment

for schizophrenia, consisting essentially of, in a concentration expressed as % by weight of the total fatty acid weight in the composition, one selected from the group consisting of: a) ALA ethyl ester, wherein ALA ethyl ester is present in a concentration not lower than 70%, b) DHA ethyl ester >30 and EPA ethyl ester >44, wherein EPA+DHA ethyl esters >80, the ethyl esters of other (C20, C21, C22) n-3 acids being >3, and c) DHA ethyl ester >34 and EPA ethyl ester >40, wherein EPA+DHA ethyl esters >80, the total ethyl esters of n-3 acids being >90; and at least another drug effective for the treatment of schizophrenia."

Applicant submits that, in view of the amendments presented herein, this rejection is no longer applicable. Applicant asserts that the combination of Nishikawa *et al.,* Horrobin and Chen does not render the presently amended claims obvious because none of Nishikawa *et al.*, Horrobin and Chen provide an implicit or explicit motivation to a skilled person to modify their teachings such that they result in the presently claimed invention, and because the teachings of the prior art would discourage one from attempting to treat schizophrenia as currently claimed, i.e., the prior art *teaches away* from the presently claimed invention. In addition, the presently claimed composition exerts a synergistic effect in combination with drugs such as, e.g., clozapine, and the results of the presently claimed invention were unexpected in view of the prior art and the conventional wisdom at the time the application was filed.

Nishikawa *et al.* discloses the use of DHA and derivatives thereof in the treatment of psychosis. No mention is made of EPA being present in the composition. In view of the present amendments to the claims, Applicant submits that this document is not pertinent because in the present invention, DHA is not used on its own, but with EPA. Therefore, the person skilled in the art would not have arrived at the present invention on the basis of this reference because it describes the use of DHA and its derivatives alone. Starting from this reference, the person skilled in the art would not have been motivated to add EPA in the composition.

Turning now to the reference of Horrobin, the Examiner states that it exemplifies a capsule containing 200 mg purified GLA and 200 mg purified EPA for the treatment of schizophrenia, 2-8 capsules per day, giving a daily dosage of EPA in the range of 400-1600 mg per day. The composition can include vitamin E. Claim 29 has been amended herein to recite

"consisting essentially of" instead of "comprising," and thus does not contemplate the presence of GLA.

In view of the present amendments to claim 29, it should be noted that Horrobin discloses that the presence of an n-6 fatty acid in the composition is necessary and indispensible for this particular pharmaceutical use (see column 2, lines 24-26 in conjunction with the Table). All the Examples of this reference make it clear that the concentration of the n-6 fatty acids in the composition should be quite considerable, in particular, not lower than that of any other component. Moreover, the conclusions of the last few lines of column 2 of Horrobin make it clear that n-6 fatty acids (in the form of evening primrose oil, which is mainly n-6 fatty acids in composition, see Table of column 5 lines, 20-28, of Horrobin) are useful for the treatment of schizophrenia, but not as much for the treatment of tardive dyskinesia (TD). The inclusion of n-3 fatty acids in Horrobin is thus justified by the need to address the treatment of TD, and n-3 fatty acids constitute in any case only a small percentage of the total composition (as better elucidated below). The teaching of Horrobin in the treatment of schizophrenia is clearly in the direction of the use of large concentrations of n-6 fatty acids, which in all instances constitute at least 50% of the composition.

The differences between the presently claimed invention and Horrobin are made clear also from the Examples in Horrobin (column 6). Capsules A1 include 50% evening primrose oil (EPO, which is composed mainly of omega-6 fatty acids – see column 5, lines 20-28 of Horrobin) and 50% fish oil (only 18% EPA and 12% DHA in the fish oil and consequently 9 and 6% respectively in the whole composition). Capsules A2 contain GLA and EPA in a 1:1 ratio. Capsules B3 contain 50% EPO and 50% fish oil. Capsule B4 contain 300 mg AA, 300 mg DHA and 75 mg vitamin E. Capsules B5 contain GLA, DGLA, AA, stearidonic acid, EPA and DHA in equal proportions, plus vitamin E. None of these Examples of Horrobin therefore fall within the scope of claim 29 as presently amended.

Applicant submits that the possibility of using vitamin E is devoid of any significance, because the usual low doses (e.g. 0.03, 0.3 or 0.4%) have the sole function of stabilizing compositions and formulations *in vitro*, whereas only substantially higher doses, e.g. >10%, may have a significance *in vivo*, in both cases with a poor correlation with the activity on

schizophrenia. Therefore, the person skilled in the art and considering Horrobin would have found no teachings in the direction of the present invention. In fact, the analysis of the reference would have probably directed the skilled person away from the solution of the present invention. In this respect, please also refer to the additional data included in the 1.132 Declaration filed September 24, 2010. As described in the 1.132 Declaration, this data demonstrates that the combination EPA + DHA of the present invention has a higher activity compared to MaxEpa (18% EPA and 12% DHA and a component of the capsules A1 by Horrobin – high in omega-6, low in omega-3), ascribable to the greater concentration of the active ingredients in the composition.

Turning now to Chen et al., this document was cited because it teaches that schizophrenia encompasses paranoid, disorganized, catatonic and undifferentiated schizophrenia. The substances described in Chen et al. are completely unrelated to the presently claimed active substances. Applicant asserts that this reference fails to cure any of the deficiencies of Nishikawa *et al.* or Horrobin.

Applicant asserts that the person skilled in the art *combining* the teachings of Nishikawa *et al.* and Horrobin would not have arrived at the invention of the present application. Nishikawa *et al.*, in fact, contemplates the use of DHA and derivatives, alone, for the treatment of psychosis. Horrobin, on the other hand, teaches that a considerable amount (at least 50%) of omega-6 fatty acids should be present in a composition for there to be a satisfactory effect in the treatment of schizophrenia (considered to be a form of psychosis). The person skilled in the art starting from the composition of Nishikawa *et al.* and considering Horrobin would have been induced to introduce omega-6 fatty acids to the composition of Nishikawa *et al.* so as to constitute at least about 50% of the fatty acid contribution to the composition (see the Examples of Horrobin). In the present invention, such a high contribution from omega-6 fatty acids is not contemplated. As a consequence, the skilled person would not have arrived at the high concentration of EPA + DHA of the present invention (over 80% w.b. on the total weight of fatty acid esters). The person skilled in the art and combining these teachings would thus have made a combination that was different and not as effective as that of the present invention.

Likewise, the person skilled in the art starting from the composition of Horrobin and considering Nishikawa *et al.* would not have arrived at the composition of the present invention because Horrobin teaches the importance and efficacy of omega-6 fatty acids. The skilled person would thus not have renounced omega-6 fatty acids in favour of DHA or DHA + EPA in a concentration higher than 50% or higher than the contribution of the omega-6 fatty acids. This skilled person would thus not have arrived at the composition of the present invention. In either case, the combination of the references would not have induced the skilled person to use the high EPA + DHA concentration of the present invention as there are no teachings in this respect. In both cases, moreover, the person skilled in the art would not have been induced to combine the components from their individually known common utility (as stated by the Examiner on page 13 of the Office Action, lines 1 and 2, with reference to Kerkhoven, 205 USPQ 1069 (CCPPA 1980)) because the prior art does not provide a clear teaching in this respect. As a consequence, the usefulness of the compounds used in the present invention could not have been considered to be known to artisan. Based on the above, Applicant asserts that the claims as amended herein are thus novel and non-obvious over the cited prior art.

Further, regarding the Examiner's assertion that Nishikawa *et al.* show improvements in both the positive and the negative symptoms of schizophrenia, it is respectfully pointed out that this does not seem to be the case. As previously argued, in the *in vivo* test, a direct clinical test, it was ascertained that a one-month treatment with 3x300 mg DHA brought to improvements of the negative symptoms of schizophrenia in the majority of the treated subjects. Nothing more is said apart from the fact that neither primary side effects nor significant variations in biochemical blood and urine tests were detected and that a reduced total cholesterol and an increased HDL-cholesterol was found, although with no significant differences in these values. Therefore, a skilled reader (contrary to what is stated by the Examiner on page 11, last few lines) would certainly conclude that no improvement of the positive symptoms has been ascertained. Differently from the negative symptoms, the positive symptoms comprise behavior disorders and the inability to think in a coherent manner, associated with abnormal sensations (allucinations) and illusory beliefs (delusions), and are characterized by psychomotor excitation. Applicant's experiments on mice (see Example 6 in the application as-filed, and the new data included in the

1.132 Declaration filed September 24, 2010) have instead demonstrated that the compositions according to the present invention can counteract the induced schizophreniform psychosis (hyperactivity and excitatory-toxic effects, which are typical of the positive syndrome).

With reference to the issue, raised by the Examiner, that Nishikawa *et al.* describe the use of DHA in conjunction with other antipsychotics, it is respectfully argued that the reference does not describe a treatment combining the use of the composition with an antipsychotic (please see Example 2 of Nishikawa et al. where it is stated that "eleven out of sixteen subjects had been treated with chlorpromazine and haloperidol in the past", not in the Example being described). There is thus no proof in Nishikawa *et al.* that there is a synergistic action between DHA and haloperidol. By contrast, the composition of the present invention (see claims 48 and 49 as amended herein) exerts a synergistic effect in combination with drugs such as, for example, clozapine. This is shown in the data included in the 1.132 Declaration filed September 24, 2010.

As asserted above, the prior art *teaches away* from using DHA alone, and to use instead EPA, but not in association with DHA. Applicant is aware that when rejecting a claim based on a motivation to combine, an explicit suggestion to combine the prior art is not necessary, and that the motivation to combine may be implicit and may be found in the knowledge of one of ordinary skill in the art. However, in the instant combination of references, one of ordinary skill in the art would find no motivation, implicit or explicit, to alter the methods of Nishikawa *et al.*, based on Horrobin's disclosure that an n-6 acid is necessary in a composition for treating schizophrenia, and Chen's disclosure of different types of schizophrenia. In view of the prior art's *teaching away* and the conventional wisdom at the time the invention was made, the presently claimed invention is non-obvious and inventive over the prior art.

New claim 50 recites a "method of using a composition, for the preparation of a drug for the treatment of schizophrenia, consisting essentially of, in a concentration expressed as % by weight of the total fatty acid weight in the composition, ALA ethyl ester, wherein ALA ethyl ester is present in a concentration not lower than 70%." Applicant submits that the combination of Nishikawa *et al.*, Horrobin and Chen also fails to render new claim 50 obvious because none of Nishikawa *et al.*, Horrobin and Chen provide an implicit or explicit motivation to a skilled person to modify their teachings such that they result in the presently claimed invention.

Based on the foregoing, Applicant submits that the combination of Nishikawa *et al.*, Horrobin, and Chen does not render the present invention obvious within the meaning of 35 U.S.C. 103. Each reference fails to implicitly or explicitly suggest modifying its teachings to arrive at Applicant's invention, the prior art actually *teaches away* from the claimed invention, and the results of the presently claimed invention were unexpected in view of the prior art.

Accordingly, withdrawal of this rejection is respectfully requested.

Conclusion

The currently pending claims before the Examiner are supported throughout the specification and are patentable over the prior art. No new matter has been added. This application is now in full condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge the $130.00 fee for a two month extension of time and the required fee for the RCE filed herewith to the attached credit card authorization. Although no additional fees are believed due, the Commissioner is hereby authorized to charge any deficiency or credit any surplus to Deposit Account No. 14-1437.

The Examiner is cordially invited to call the undersigned if clarification is needed on any matter within this amendment, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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/Amy A. Dobbelaere/

Amy A. Dobbelaere, Ph.D.
Reg. No. 52,088
NOVAK DRUCE + QUIGG
525 Okeechobee Blvd, 15th Floor
West Palm Beach, FL 33401
Telephone: (561) 847-7809

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